REMARKS

Reconsideration of the rejection of elected claim 19 and rejoinder of withdrawn claims 24 and 26 are respectfully requested in view of the above amendments and the following remarks.

Claim Amendments

Elected claim 19 has been amended by replacing the "method of preventing or treating atherosclerosis" with a "method of treating or reducing the extent of atherosclerosis." Support for this amendment is found in the "Results" portion of the specification at page 10.

Non-elected claims 20-23 and 25 have been newly cancelled. Applicant previously elected the invention of Group III (claims 19-26 drawn to various method procedures) for prosecution in this application. The restriction requirement made in the Action of November 16, 2007 required that if Applicant elected the invention of Group III, that Applicant must also elect "a single disclosed method specie disclosed in instant claims 19-26." More specifically, the Examiner stated in the last paragraph on page 4 of that Action that:

> Within the method species (claims 19-26), applicant must elect either (1) a method of preventing or treating atherosclerosis, (2) a method of preventing cardiovascular events, (3) a method of preventing or treating an inflammatory disease or condition, (4) a method in inhibiting expression of (i) CD40 or (ii) metalloproteinases (MMPs) or (iii) LOX-1, or (5) a method of treating atherosclerosis.

The Examiner further noted at page 5 of that Action that upon allowance of a generic claim, Applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim.

In response to this request for election of species, Applicant elected species (1), "a method preventing or treating atherosclerosis," being claim 19, and claims 20-26 directed to the non-elected species were maintained but designated as "withdrawn" (Applicant's Response to Restriction Requirement and Second Preliminary Amendment filed February 15, 2008).

In order to simplify the issues and to expedite the prosecution of this application, the above amendments now cancel withdrawn claims 20-23 and 25. Upon further review of the claims, it appears to the undersigned that no pending claim is generic to all of claims 19-26, in which case rejoinder of many of claims 20-26 with presently elected claim 19 seems unlikely. Therefore, withdrawn claim 20 (method of preventing cardiovascular events), claims 21 and 22 (method of preventing or treating an inflammatory disease or condition), claim 23 (method of inhibiting expression of CD40 and/or metalloproteinases (MMPs) and claim 25 (method of inhibiting expression of LOX-1) have been cancelled.

However withdrawn claim 24 (method of treating atherosclerosis ... by inhibition of expression of CD40 and/or metalloproteinases (MPPs)) and withdrawn claim 26 (method of treating atherosclerosis ... by inhibition of expression of LOX-1) appear to be species of elected claim 19, directed toward (as amended above) a "method of treating or reducing the extent of atherosclerosis." Inasmuch as claims 24 and 26 are also directed toward a method of treating atherosclerosis, it seems appropriate that they be rejoined with method claim 19 for prosecution in the present application, now or at least upon allowance of claim 19.

It should be clear from the above that no new matter has been added by the above amendments. These amendments are being made without waiver or prejudice to Applicant's right to prosecute any subject matter thereby deleted in one or more divisional or continuing applications.

Following entry of these amendments, claims 19, 24 and 26 are pending in this application with claims 24 and 26 being designated as "withdrawn."

Claim Rejections Under 35 U.S.C. § 112, Paragraph 1

Claim 19 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating atherosclerosis, does not reasonably provide enablement for preventing atherosclerosis. At page 4 of the specification the Examiner points out that the results portion of the experimentation (pages 10 and 11 of the specification) discloses reduction and inhibition but that embodiments or models adequately and substantially supporting preventative results are absent.

While Applicant does not necessarily agree with the Examiner's position, elected claim 19 has been amended above to be directed toward a "method of treating or reducing the extent of atherosclerosis." Support for this amendment is found in the "Results" portion of the specification at page 10, and it is respectfully submitted that the experimental data presented therein clearly enables claim 19 as presently amended. Accordingly, it is believed that this ground for rejection has been overcome.

Claim Rejections Under 35 U.S.C. § 103

Claim 9 [it is assumed the Examiner meant elected claim 19] is rejected under 35 U.S.C. 103(a) as being unpatentable over Qin *et al.* "Effects of the combination of an angiotensin II antagonist with an HMG-CoA reductase inhibitor in experimental diabetes" (hereinafter "Qin *et al.*"), in view of Leyland-Jones, published US application 20030053950 A1 (hereinafter "Leyland-Jones") and Robl, US Patent 6,620,821 B2 (hereinafter "Robl '821"). The Examiner cites (and provides a copy of) only the abstract of Qin *et al.* For completeness of the record, Applicant has obtained and submits herewith a full copy of the Qin *et al.* reference.

Qin *et al.*

Qin *et al.* is cited as teaching the effects of an angiotensin II antagonist in combination with an HMG-CoA reductase inhibitor.

More specifically, Qin *et al.* tested the possible effects of the combination of an angiotensin II antagonist (losartan) with an HMG-CoA reductase inhibitor (simvastatin) *in diabetic kidney injury*, *e.g.*, progressive renal disease associated with diabetic nephropathy. There is *no mention* in the full copy of this reference of atherosclerosis and *no mention* of either rosuvastatin or candesartan or any combination thereof, to which the presently claimed method is directed. Moreover, it is apparent from the disclosure of this reference at page 565, left column under "Results," that the amount of the drugs used in the paper was not sufficient to give any effect on plasma concentration of cholesterol or triglycerides. See also page 570, left column, end of the second full paragraph, noting that the effects of simvastatin in this test "occurred in the setting of no significant influence on plasma cholesterol and triglycerides" and that "these findings support the view that

statins may confer renal protection independent of their effects as lipid-lowering agents." It is therefore respectfully submitted that the nature of the study disclosed in this reference would not suggest or motivate the skilled person toward testing an angiotensin II antagonist in combination with a statin for treatment of atherosclerosis.

The Examiner correctly acknowledges at page 7 of the Action, fourth full paragraph, that Qin *et al.* "does not teach the combination of these bioactive agents for atherosclerosis," and therefore additionally cites Leyland-Jones.

Leyland-Jones

The Examiner cites Leyland-Jones, specifically paragraph [0181], as disclosing "rosuvastatin (Crestor) as a drug of choice for congestive heart failure of which atherosclerosis is indicated as a contributing and associative disease state." This characterization of the disclosure of this reference is respectfully traversed.

First of all, paragraph [0181] of Leyland-Jones does *not* disclose "rosuvastatin (Crestor) as a *drug of choice*" (emphasis added), but states that "the *statin class of drugs* has revolutionized the prevention of CHD ..." Seven statins are specifically named: lovastatin, simvastatin and pravastatin are characterized as the "original three statins"; and fluvastatin, atorvastatin and cerivastatin are characterized as "the three newest statins"; and rosuvastatin is simply characterized as "the most recent statin." It is respectfully submitted that the wording of paragraph [0181] does not support the Examiner's characterization of its disclosure, that rosuvastatin is "the drug of choice for congestive heart failure." Moreover, paragraph [0184], also cited by the Examiner, gives dose ranges and efficacy for various of the statins, but does not mention rosuvastatin.

It should further be noted that these paragraphs concerning HMG-CoA reductase inhibitors (paragraphs [0181] - [0187]) make *no mention of atherosclerosis*. On the other hand, the paragraphs that the Examiner cites as dealing with atherosclerosis *make no mention of HMG-CoA reductase inhibitors*. Thus paragraph [0023], cited at the bottom of page 7 of the Action as disclosing atherosclerosis, is in the section of this reference concerned with vitamin D, with atherosclerosis being mentioned as one of many disease conditions that can be effected by deficiencies in vitamin D 25-hydroxylase. Paragraph [0104], also cited at the bottom of page 7 of the Action as disclosing atherosclerosis, is in

the section of this reference headed "Phosphotriesterases," which concludes with the statement, "some studies have also implicated phosphotriesterase in atherosclerosis and diseases involving lipoprotein metabolism." The only other mention of atherosclerosis in this entire reference is in paragraph [0017] noting that "mutations in cytochromes p450 have been linked to metabolic disorders, including ... atherosclerosis ...." It is respectfully submitted that none of these mentions of atherosclerosis in Leyland-Jones has any relation to the present invention, and this reference would not suggest use of the presently claimed method for atherosclerosis.

It is therefore not seen what this reference adds to Qin *et al.* with respect to the present presently claimed method for the treatment or reduction of the extent of atherosclerosis by administering a combination of rosuvastatin and candesartan.

Moreover, as the Examiner notes at page 8 of the Action, Leyland-Jones does not teach *candesartan* for the treatment and/or prevention of atherosclerosis, and therefore the Examiner draws on Robl '821.

Robl '821

Robl '821 is directed toward new HMG CoA reductase inhibitors of formula I as disclosed in detail in columns 1 through 27 of this reference. The reference then notes in the middle of column 28 that the "HMG CoA reductase inhibitors of formula I may be employed in combination with all therapeutic agents which are useful in combination with HMG CoA reductase inhibitors." The reference then provides, in columns 28 through 39, what virtually amounts to a shopping list of possible combination products. Amongst this very extensive disclosure of diverse types of other therapeutic agents there is a discussion extending from column 35, line 62 through column 37, line 61 of various types of "antihypertensive agents which may be employed in combination with the HMG CoA reductase inhibitors of the invention," including ACE inhibitors, angiotensin II receptor antagonists, NEP inhibitors, NEP/ACE inhibitors, calcium channel blockers, T-channel calcium antagonists, β-adrenergic blockers, diuretics, α-adrenergic blockers, dual action receptor antagonists, heart failure drugs and "other types of antihypertensive agents."

The angiotensin II receptor antagonists are specifically discussed at column 37, lines 16-20 as follows:

> The angiotensin II receptor antagonist (also referred to herein as angiotensin II antagonist or AII antagonist) suitable for use herein includes, but is not limited to irbesartan, losartan, valsartan, candesartan, tasosartan or eprosartan, with irbesartan, losartan or valsartan being preferred.

This is the *only* mention of candesartan in the entire Robl '821 disclosure, as one of six AII antagonists, the AII antagonists being only one of nine or more *types* of antihypertensive agents, the antihypertensive agents being only one of the multitude of other *types of therapeutic agents* extensively listed over 11 columns of the disclosure. Candesartan is not even one of the three preferred AII antagonists, as noted in the above-quoted passage.

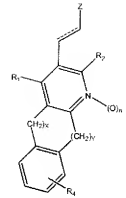
Moreover, focus of the disclosure is on certain *new* HMG CoA reductase inhibitors of formula I, and there is no suggestion that any *other* HMG CoA reductase inhibitor be combined with one of this multitude of other therapeutic agents, no less rosuvastatin.

The undersigned wishes to further comment on the Examiner's statements with regard to the Robl '821 reference to be certain that there is no misunderstanding on the record. At page 8 of the Action, third full paragraph, the Examiner seems to be citing the Abstract of Robl '821 as disclosing that candesartan is of the structure given in the abstract, and thus is an HMG CoA reductase inhibitor. Specifically, the Examiner states:

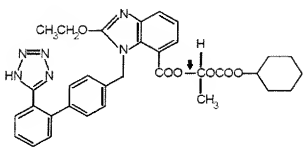
> However, Robl ***does teach candesartan*** as a compounds ***of the following structure*** are HMG CoA reductase inhibitors and thus are active in inhibiting cholesterol biosynthesis, modulating blood serum lipids, for example, lowering LDL cholesterol and/or increasing HDL cholesterol, and treating hyperlipidemia, dyslipidemia, hormone replacement therapy, hypercholesterolemia, hypertriglyceridemia and atherosclerosis [...] and pharmaceutically acceptable salts thereof [...] (abstract only).

(Action of April 30, 2008 at page 8, third full paragraph; bold italicized emphasis added, brackets in original).

The structure given in the abstract is as follows:



whereas the structure of candesartan is as follows:



Therefore, the above-quoted statement by the Examiner is not understood. The structure of candesartan does not appear anywhere in this reference and, in fact, the word "candesartan" appears only once, at column 37, line 19, as noted by the Examiner at page 8 of the Action and discussed above.

In view of the above discussion of the references applied to the obviousness rejection, it is respectfully submitted there is no reasonable reading of the applied references, either alone or in combination, that suggests the presently claimed invention of treating or reducing the extent of atherosclerosis in a warm blooded animal by administration of an effective amount of a combination comprising candesartan and rosuvastatin. However, *even if* one were to assert that these applied references gave rise to *prima facie* obviousness, it is respectfully submitted that the comparative evidence provided in the present specification, demonstrating the unexpected synergistic anti-atherosclerotic effect of the combination of candesartan and rosuvastatin relative to either agent alone, overcomes any such *prima facie* obviousness. In this regard the Examiner's attention is called to the details of the experiment set out beginning at page 7, line 17 of

the specification, the results verbally stated beginning at page 10, line 7, and the graphic illustration of this synergistic anti-atherosclerotic effect in Figure 2 at page 12 of the specification.

It is therefore respectfully submitted that this obviousness rejection has been overcome and should be withdrawn.

International Preliminary Examination Report

Attached hereto is the Written Opinion of the International Searching Authority issued in the PCT application of which the present application is the US National Stage. Each reference discussed therein was cited in the International Search Report. A further copy of the International Search Report is also attached for the Examiner's convenience. Each such reference was formally cited (and a copy provided) with the Information Disclosure Statement filed March 24, 2006, except for the Chen literature reference, which was inadvertently omitted but later formally cited (and copy provided) with the Supplemental Information Disclosure Statement filed June 22, 2006. A copy of the Internal Search Report was filed herein with the Information Disclosure Statement of March 24, 2006.

The Examiner will note that documents D3 (EP1314425), D4 (WO95/26188) and D5 (JP 200214577; abstract) were specifically discussed in the Written Opinion, which concluded that the subject-matter of claims 1 to 11 seems to be novel and to involve an inventive step. It is noted in Section VI of the Written Opinion that documents D1 (Chen et al.) and D2 (WO2004/96810) were not considered to constitute prior art, and they do not constitute prior art to the present application inasmuch as their prior art effective dates are later than the September 26, 2003 priority date to which the present application is entitled.

It is understood that the Examiner has considered each of these references, as acknowledged by the initialed copy of the forms PTO-1449, filed March 24, 2006 and June 22, 2006, returned with the US PTO paper mailed June 11, 2008.

Information Disclosure Statement

The Examiner's attention is drawn to the further Information Disclosure Statement that is submitted herewith, together with a form PTO-1449 citing two documents cited in a foreign corresponding application and also citing the full copy of the Qin *et al.* reference noted above, to supplement the abstract of such reference that was cited and provided by the Examiner. A copy of each cited document (except for the published US application) is provided with this Information Disclosure Statement.

Conclusion

All grounds for rejection have been addressed and, it is believed, overcome by the above amendments and the foregoing remarks. It is therefore respectfully requested that elected claim 19 be allowed, and that related withdrawn claims 24 and 26 be rejoined and allowed in this application.

EXCEPT for issue fees payable under 37 C.F.R. § 1.18, the Director is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. §§ 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-0310. This paragraph is intended to be a **CONSTRUCTIVE PETITION FOR EXTENSION OF TIME** in accordance with 37 C.F.R. § 1.136(a)(3).

Respectfully Submitted,
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REC'D 16 MAR 2005
WIPO PCT

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

7/4 (64)

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)	
Applicant's or agent's file reference see form PCT/ISA/220	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB2004/004120	22.09.2004	26.09.2003

International Patent Classification (IPC) or both national classification and IPC
A61K31/505, A61K31/4184

Applicant
ASTRAZENECA UK LIMITED

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:
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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/GB2004/004120

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 8, 9

because:

☒ the said international application, or the said claims Nos. 8, 9 relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the whole application or for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-11
	No: Claims	
Inventive step (IS)	Yes: Claims	1-11
	No: Claims	
Industrial applicability (IA)	Yes: Claims	1-7, 10, 11
	No: Claims	8,9 (see section V)

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

see form 210

Section III:

Claims 8 and 9 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Section V:

Subject-matter

The present application discloses the combination of candesartan and rosuvastatin and their use (for prevention or treatment of atherosclerosis/cardiovascular "events").

Prior art

Reference is made to the following documents:

D3 (EP1314425) relates to pharmaceutical compositions for the prevention or treatment of cardiac failure, the prevention of ischemic coronary heart disease or the prevention of the recurrence of ischemic coronary heart disease, said pharmaceutical compositions containing a HMG-CoA reductase inhibitor selected from the group consisting of pravastatin, simvastatin, lovastatin, pitavastatin and ZD-4522 and an angiotensin II receptor antagonist and optionally further containing a calcium channel blocker (1/[0001]).

D4 (WO95/26188) discloses the combination of HMG-CoA reductase inhibitor and an angiotensin II receptor antagonist for the treatment of atherosclerosis (1/6-16; claim 1)

D5 (JP2002145770) is directed to the use of a HMG-CoA reductase inhibitor together with an angiotensin II receptor antagonist for the treatment of heart diseases (abstract).

The numbering results from the order of citations found in the Search Report.

Novelty

In view of the prior art as summarized above the subject-matter of claims 1 to 11 seems to be novel und Article 33 (2) PCT.

Inventive step

The subject-matter of claims 1 to 11 seems to involve an inventive step in the sense of Article 33 (3) PCT.

D3 which is the closest prior art differs from the present invention only in that it does not suggest the claimed combination as such. It gives a list of HMG-CoA reductase inhibitors and angiotensin II receptor antagonists.

The problem to be solved can be described as how to provide further medicaments for the treatment of atherosclerosis.

None of the prior art documents suggests the claimed combination. However, the applicant has shown an synergistic effect of the combination of candesartan and rosuvastatin (= ZD-4522) (see Fig.). Therefore, the claimed combination seems to be inventive.

Clarity

The term "cardiovascular events" is unclear (Article 6 PCT).

Industrial applicability

For the assessment of the present claims 8 and 9 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Section VI:

Although D1 and D2 (Chen et al. and WO2004/96810) do not constitute prior art within the meaning of Rule 64.1 (b) PCT, it appears to disclose all the features of claims 1 to 11 of the present application.

INTERNATIONAL SEARCH REPORT

Interna tional Application No
PCT/GB2004/004120

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/505 A61K31/4184

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	CHEN JIAWEI ET AL: "Marked upregulation of lipoxygenase-1, a receptor for ox-low-density lipoprotein in atherosclerosis, and its total ablation by candesartan and rosuvastatin given concurrently." JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY, vol. 43, no. 5 Supplement A, 3 March 2004 (2004-03-03), page 498A, XP002319611 & 53RD ANNUAL SCIENTIFIC SESSION OF THE AMERICAN COLLEGE OF CARDIOLOGY; NEW ORLEANS, LA, USA; MARCH 07-10, 2004 ISSN: 0735-1097 abstract ----- -/--	1-11

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
9 March 2005	18/03/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Heller, D

Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

Intern onal Application No
PCT/GB2004/004120

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 2004/096810 A (PFIZER LIMITED; BELL, ANDREW, SIMON; BROWN, DAVID, GRAHAM; FOX, DAVID,) 11 November 2004 (2004-11-11) claims 1-22	1-11
Y	EP 1 314 425 A (SANKYO COMPANY, LIMITED) 28 May 2003 (2003-05-28) page 1, paragraph 1	1-11
Y	WO 95/26188 A (MERCK & CO., INC; NELSON, EDWARD, B; SWEET, CHARLES, S) 5 October 1995 (1995-10-05) page 1, lines 6-16 claim 1	1-11
Y	PATENT ABSTRACTS OF JAPAN vol. 2002, no. 09, 4 September 2002 (2002-09-04) & JP 2002 145770 A (SANKYO CO LTD), 22 May 2002 (2002-05-22) abstract	1-11

Form PCT/ISA/210 (continuation of second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern onal Application No
PCT/GB2004/004120

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2004096810 A	11-11-2004	WO 2004096810 A1	11-11-2004
		NL 1026074 A1	01-11-2004
		US 2005043325 A1	24-02-2005
EP 1314425 A	28-05-2003	AU 8441301 A	13-03-2002
		CA 2420844 A1	28-02-2003
		EP 1314425 A1	28-05-2003
		US 2003181500 A1	25-09-2003
		WO 0217913 A1	07-03-2002
		JP 2002145770 A	22-05-2002
WO 9526188 A	05-10-1995	AU 696868 B2	17-09-1998
		AU 2127995 A	17-10-1995
		CA 2186606 A1	05-10-1995
		EP 0754042 A1	22-01-1997
		JP 9510973 T	04-11-1997
		WO 9526188 A1	05-10-1995
		US 5663186 A	02-09-1997
		US 5663187 A	02-09-1997
JP 2002145770 A	22-05-2002	AU 8441301 A	13-03-2002
		CA 2420844 A1	28-02-2003
		EP 1314425 A1	28-05-2003
		WO 0217913 A1	07-03-2002
		US 2003181500 A1	25-09-2003